

# A Case of Immunoglobulin E Mediated Anaphylaxis to Levodropropizine

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We experienced a case of immunoglobulin E (IgE) mediated anaphylaxis to levodropropizine. The patient was an 18-year old Korean woman. After taking the common cold medication including acetaminophen, domperidone, and levodropropizine, skin rash, angioedema and anaphylaxis were developed immediately. As she was tolerable to acetaminophen alone, we thought the culprit agent was maybe a levodropropizine tablet. To confirm the culprit, she underwent skin prick test and oral drug provocation test with the suspected one. Finally we detected levodropropizine specific IgE and confirmed the specificity by inhibition enzyme-linked immunosorbent assay (ELISA).

**Key Words:** Levodropropizine, anaphylaxis, drug hypersensitivity

## INTRODUCTION

Levodropropizine is widely used peripheral acting antitussives. It suppresses cough through inhibition of vagal C-fiber and its neuropeptide.<sup>1</sup> Previously reported adverse drug reactions of levodropropizine were nausea, diarrhea and epigastric discomfort.<sup>2</sup> Only two cases of anaphylaxis to levodropropizine were reported,<sup>3,4</sup> but the mechanism of levodropropizine anaphylaxis is not yet clarified. We experienced a case of anaphylaxis after taking levodropropizine tablet and confirmed the causality with oral provocation test. Furthermore, we confirmed the presence of levodropropizine specific immunoglobulin E (sIgE) with skin prick test, enzyme-linked immunosorbent assay (ELISA) and inhibition ELISA tests. These findings suggest that levodropropizine can induce anaphylaxis through the IgE-mediated immune mechanism.

## CASE REPORT

An 18-year old Korean woman visited outpatient clinic because of recurrent collapse after taking common cold medication. She experienced generalized itching sensation followed by skin rash and angioedema, and collapse after common cold

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medication twice before. Her recent medication included acetaminophen, domperidone and levodropropizine 60 mg. When she took a pain killer including acetaminophen, caffeine, or isopropylantipyrine (Geworin®, Samjinpharm CO., LTD, Seoul, Korea), she did not experience any allergic symptoms. She had no history of any other medical illness including allergic disease. And she had no family history of allergic disease.

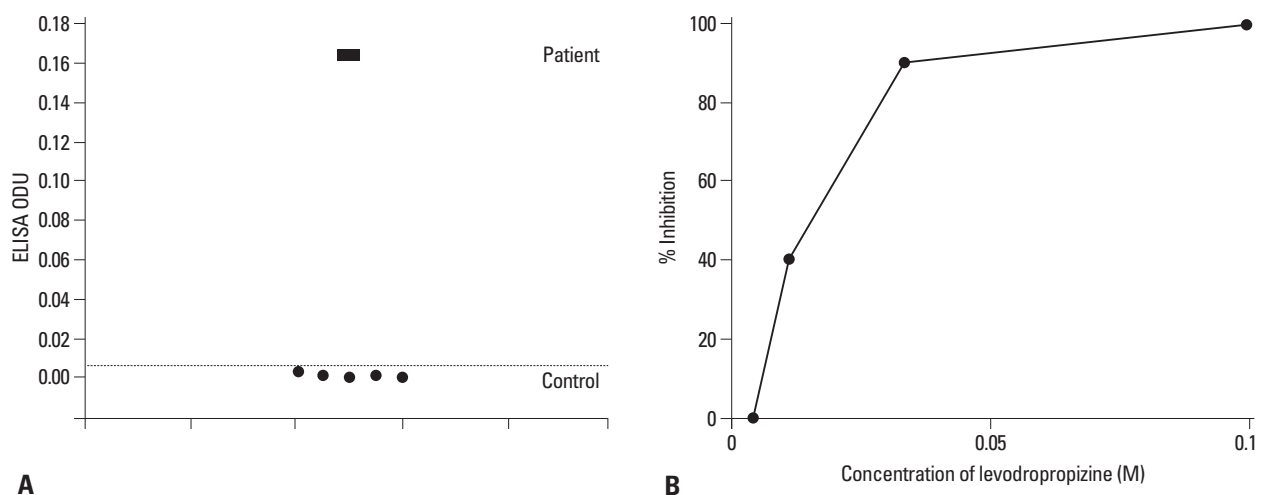
Skin prick tests were found to be positive with levodropropizine, whereas skin prick tests and intradermal tests with antibiotics [Penicillin-G (Hanall biopharma, Seoul, Korea), Cefazolin (Yuhan Corporation, Seoul, Korea), Amoxicillin (Ilsung pharmaceuticals, Seoul, Korea)] were negative. We used levodropropizine syrup (Levotuss syrup®, Hyundai-pharm. CO., LTD, Seoul, Korea) for skin prick test, started with levodropropizine 0.06 mg/mL (1 : 100 dilution in saline) and mean diameter of wheal was 4 mm to levodropropizine 0.06 mg/mL (10% histamine in phenol saline: 6 mm, 0.9% saline: negative, levodropropizine 0.6 mg/mL: 5 mm, levodropropizine 6.0 mg/dL: 6.5 mm). She had no specific IgE antibodies to antibiotics including penicilloyl G, amoxicilloyl, ampicilloyl, and cefaclor by Immuno CAP® (Phadia AB, Uppsala, Sweden) method. Skin prick test for common inhalant allergens was not done. Oral provocation tests were performed to confirm the causative drug with 1 hour interval for each agent. We used levodropropizine syrup (Levotuss syrup®, 6 mg/mL, 1/30 of recommended daily dose) and started with 6 mg. After taking 6 mg of levodropropizine, she had no specific symptom and signs for an hour. Therefore, she took 12 mg

of levodropropizine. After 2 minutes, she felt generalized itching sensation, and throat swelling, and skin rash was developed at anterior chest wall. We injected 1 : 1000 epinephrine 0.3 mL intramuscularly. She didn't experience anaphylaxis. In addition, 625 mg of acetaminophen open oral provocation test was negative.

We also measured levodropropizine sIgE in the patient's serum by ELISA. A 96-well polystyrene plate (Costar, Tewksbury, MA, USA) was coated with 40 µg/mL of human serum albumin and incubated overnight. After blocking with skim milk, pure levodropropizine provided by Hyundai-pharm.Co., Ltd. (Manufacture of Levotuss syrup®). 0.5-100 mM 50 µL conjugated with EDC (Thermo scientific, Rockford, IL, USA) 50 µL was added, and patient serum and anti-human IgE were incubated for 1 hour each step. After washing, 1 : 1000 biotin-labeled anti-human IgE (Vector Laboratories Inc., Burlingame, CA, USA), Streptavidin-HRP (R&D systems, Minneapolis, MN, USA), TMB (Tetramethylbenzidine, KPL, Gaithersburg, MD, USA) were added to each well.

The level of sIgE to levodropropizine was 0.166 optical density units reading at the 405-nm ultraviolet wavelength by an automated microplate spectrophotometer (Fig. 1A). For inhibition ELISA, patient serum was preincubated for 1 day before and being measured in the ELISA performed before. The results showed dose-dependent inhibition pattern: At 0.1 M concentration, it showed complete inhibition (Fig. 1B).

We concluded that culprit of anaphylaxis was levodropropizine. The patient was educated to avoid levodropropizine. Since now she never experienced any allergic symptoms.



**Fig. 1.** (A) Level of levodropropizine-specific immunoglobulin (Ig) E in healthy controls and patient serum. Control serum 0.001 OD, patient serum 0.166 OD, respectively. (B) Inhibition ELISA using levodropropizine as the inhibitor. Levodropropizine showed dose-dependent inhibition pattern. At 0.1 M concentration, it completely inhibited the binding of specific IgE to levodropropizine-HSA conjugate. ODU, optical density unit; HSA, human serum albumin; ELISA, enzyme-linked immunosorbent assay.

## DISCUSSION

Antitussive agents are divided into two groups by their action sites. Centrally acting antitussives include narcotic opioid (morphine, codein), non-narcotic opioid (dextromethorphan) and nonopioid (benproperine, zipeprol), and peripherally acting cough suppressant includes benzonatate, and levodropropizine. Previous clinical studies showed that levodropropizine is as effective as centrally acting cough suppressant such as codein<sup>2</sup> and dextromethorphan.<sup>5</sup> However, levodropropizine has been regarded safer than centrally acting antitussives in terms of central side effects such as somnolence and sedation.<sup>6</sup> Therefore, it is widely given to acute or chronic bronchitis patients.

Previously reported adverse drug reactions of levodropropizine were nausea, vomiting, dyspepsia, diarrhea, fatigue, general weakness, somnolence, headache, dizziness, palpitation and rarely allergic skin reaction. Only 2 cases of anaphylaxis to levodropropizine have been reported worldwide. The first case was 41-year-old Korean man. Intradermal test and oral provocation test to levodropropizine showed positive result and basophil histamine release test was positive which indicates that direct histamine release could induce levodropropizine anaphylaxis.<sup>3</sup> The second case was 4-year old boy, and his skin prick test and oral provocation to levodropropizine was similarly positive. In addition, his tryptase level 3 hours after anaphylaxis was in upper normal range.<sup>4</sup>

In our present case, skin prick test and oral provocation test results were positive, and we also could detect sIgE to levodropropizine in patient's serum, which means that levodropropizine can induce anaphylaxis by IgE mediated mechanism. In addition, we performed ELISA inhibition test using levodropropizine as inhibitor to confirm the specificity of detected IgE, and observed dose-dependent inhibition pattern.

Levodropropizine is a small molecule (its molecular weight of 236.31), therefore, it has to be conjugated to a carrier protein for induction of IgE immune response. We used human serum albumin as the conjugator, and used it for ELI-

SA measurement. For ELISA inhibition test, we incubated the patient's serum with levodropropizine as the inhibitor, and found that it completely inhibited the specific IgE, suggesting that levodropropizine can easily form levodropropizine-carrier complex through hapten process.<sup>7</sup>

In conclusion, we report a third case of anaphylaxis to levodropropizine which might have been induced by IgE mediated immune mechanism. Therefore, we could suggest that levodropropizine as a candidate of culprit drug in addition to non-steroidal anti-inflammatory drugs and antibiotics, when anaphylaxis occurs after taking anti-cough or common cold medication.

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